REMARKS

New claims 47-107 are added to provoke interference with claims 1-61 of U.S. Application No. 09/898,398, published as U.S. publication number US 2003/0082179 A1 (Exhibit A) on May 1, 2003 under 37 C.F.R. §1.604.

New claims 47-107 are fully supported by the specification and claims as originally filed. As will be appreciated by the Office, support for all newly added claims may be found throughout the specification as an entirety, including the examples, figures and claims. No new matter has been added, and entry of the amendment is respectfully requested.

Support for new claims 47-54

For example, support for claims 47 and 51 can be found, *inter alia*, at page 11, 2nd paragraph to page 13, 1st paragraph, which teaches the use of an initial PTH sequence in itself or as "part of the wPTH complete sequence," to generate an "anti-(1-8) PTH antibody." *See also* page 3, lines 17-23, which discloses the teaching of Gao et al., *Clinica Chimica Acta* 245 (1996) 39-59 (the Gao article) (Exhibit D), and page, lines 27-28, which states that all publications or unpublished patent applications mentioned in the '639 Application are hereby incorporated by reference. *See* page 4, lines 13-19 and page 20, lines 13-14 of the '639 application (see also page 3, lines 17-23; and page 10, lines 27-28). Accordingly, the teachings of the Gao article are incorporated by reference in the present application. The Gao article teaches numerous human PTH peptides, including $hPTH_{1-34}$, $hPTH_{1-38}$ (*See* the Gao article at page 41), $hPTH_{1-33}$, $hPTH_{1-36}$, $hPTH_{1-37}$ (*See* the Gao article at page 54), and the use of $hPTH_{1-38}$ in generating anti-hPTH antibodies (*See* the Gao article at page 41). Support can be found, *inter alia*, at page 12, lines 12-22 of the present application, which teaches initial immunization, and obtaining antiserum at the end of the immunization process (*See* also page 8, line 28 to page 9, line 7 of the '422 application). Page 12, line 24 through page 13, line 4 of the present application teaches purifying anti-PTH antibody from the antiserum (*See* also page 9, lines 9-18 of the '422 application).

As explained in US 2003/0082179, "PTH is considered to be bioactive when the polypeptide is able to regulate adenylate cyclase activity." *See* page 3, paragraph 39. At page 2, lines 7-10 of the present specification it is indicated that the domain for adenylate cyclase activation comprises amino acid residues 1 to 7. The present specification clearly provides a method for producing antibodies that recognize a variety of PTH peptide fragments ranging from, PTH_{1-7} up to PTH_{1-84}, and a variety of N-terminal peptide fragments comprising the domain for adenylate cyclase activation. *See, e.g.*, page 11, line 7 to page 13, line 4 (*See* also page 8, line 24 to page 9, line 18 of the '422 application). US 2003/0082179 also indicates that a "bioactive human parathyroid hormone" includes hPTH (1-13), hPTH (1-34) and hPTH (1-84). *See* paragraph 39 of US 2003/0082179. As discussed above, the present specification teaches the step of immunizing an animal, *e.g.*, a goat, with the bioactive human parathyroid hormone such as hPTH (1-84).

What constitutes "a three-dimensional epitope of a bioactive human parathyroid hormone" is not defined in US 2003/0082179. However, US 2003/0082179 states "[i]n a preferred embodiment, the antibody recognizes and binds an epitope within the first seven amino acids of PTH, or hPTH." *See* paragraph 61 of US 2003/0082179. Accordingly, the "three-dimensional epitope of a bioactive human parathyroid hormone" includes an epitope within the first seven amino acids of PTH, or hPTH. As discussed above, the present specification teaches a method for generating "anti-(1-8) PTH antibody," which would inherently include an epitope within the first seven amino acids of PTH, or hPTH. In addition, the present specification teaches generating, recovering and isolating antibodies that specifically recognize adenylate cyclase active or "bioactive" PTH peptides. Since a bioactive PTH, *e.g.*, hPTH (1-84), presumably contains its correct three-dimensional structure, the methods taught in the present application provide methods for producing antibodies that inherently specifically recognize the three-dimensional structure of a bioactive human PTH.

Support for claim 48 can be found, *inter alia*, at page 12, lines 8-22 of the present specification, which teaches repeated administration of immunogen to generate antibodies thereto (*See also* page 8, line 24 to page 9, line 7 of the '422 application).

Support for claims 49 and 50 can be found, *inter alia*, at page 12, lines 8-22 of the present specification, which teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH), *i.e.*, between about 5000 and 10,000,000 (*See also* page 8, line 24 to page 9, line 7 of the '422 application). Although the use of KLH is not explicitly stated in the present specification, it is routinely utilized in the art as a target peptide carrier for immunization protocols at the time the present priority applications were filed (U.S. Patent Application No. 09/344,639, June 26, 1999, and U.S. Patent Application No. 09/231,422, January 14, 1999). *See, e.g.,* J.S. McMurray, *Biopolymers* 47(5):405-11 (1998) (abstract) (Exhibit E).

Support for claims 52-54 can be found, *inter alia*, at page 12, line 8 to page 13, line 4 of the present specification (*See* also page 8, line 24 to page 9, line 18 of the '422 application).

Support for new claims 55-63

Compared to claim 47, claim 55 have two differences. First, any parathyroid hormone, not just bioactive human parathyroid hormone, can be used in the immunization step. Second, claim 55 requires a second immunization step. These differences are taught in the present specification. For example, the use of PTH from various animals in addition to hPTH is taught at page 9, lines 4-11 and page 10, lines 4-14 of the present specification. The second immunization step is also taught. *See* the above discussion for claim 48. Claims 56-61 are supported by the present specification. *See* the above discussion for claims 49-54.

Support for claims 62 and 63 can be found, *inter alia*, at page 10, lines 16-20; page 11, line 7 to page 13, line 4 of the present specification (*See* also page 7, lines 6-10; page 8, line 24 to page 8, line 7 of the '422 application) which teaches the use of PTH fragments to isolate PTH

antibodies. Support for claims 62 and 63 lies in the fact that claims 62 and 63 of the present application use a genus of PTH peptides for the affinity purification step. The shortest PTH peptide in the genus is human PTH_{1-8} and the longest PTH peptide in the genus is human PTH_{1-34}. There are only 26 species in the genus, *i.e.*, PTH_{1-8}, PTH_{1-9}, PTH_{1-10}, . . .PTH_{1-34}. Under this circumstance, the genus comprising PTH_{1-13} disclosed in claims 62 and 63 of the present application provides for a description of a species within the genus. *See Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232-33 (Fed. Cir. 2000) (Description in terms of ranges of chemical properties which work in combination with ranges of other chemical properties to produce an automotive gasoline that reduces emissions was found to provide an adequate written description of [chemical components within the disclosed ranges] even though the exact chemical components of each combination were not disclosed and the specification did not disclose any distinct embodiments corresponding to any claim at issue. "[T]he Patent Act and this court's case law require only sufficient description to show one of skill in the . . . art that the inventor possessed the claimed invention at the time of filing.").

As for the PTH fragment comprising PTH_{13-34} (in claim 62), support can be found in the present specification at page 6, line 20 to page 7, line 3, which teaches the use of an antibody that specifically detects cyclase inactive PTH (CIP) fragments comprising a specific portion of PTH_{7-38}, and preferably a specific portion of PTH_{9-34}. Similar to the N-terminal PTH fragments set out above, PTH_{13-34} comprises a species within this genus. *See supra.* And, as for the PTH fragment comprising PTH_{39-84} (in claim 62), support can be found in the present specification at page 10, lines 16-20, which teaches the use of an antibody that specifically detects C-terminal PTH fragments comprising a specific portion of PTH_{39-84}.

Support for new claims 64-68

Compared to claim 55, the only difference in claim 64 is that claim 64 requires the use of 1-84 of SEQ ID NO: 1, *i.e.*, hPTH (1-84), in the immunization step. The use of hPTH (1-84) in the immunization step is taught in the present specification. For example, at page 11, 2nd

paragraph to page 13, 1st paragraph, the present specification teaches the use of an initial PTH sequence in itself or as "part of the wPTH complete sequence," to generate an "anti-(1-8) PTH antibody." The present specification supports claims 65 and 66 for the same reason that it supports claims 59 and 63 as discussed above.

The only difference between claims 64 and 67 is that claim 67 uses KLH as a carrier. As discussed above in connection with claims 49 and 50, at page 12, lines 8-22, the present specification teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH), *i.e.*, between about 5,000 and 10,000,000 (*see also* page 8, line 24 to page 9, line 7 of the '422 application). Although the use of KLH is not explicitly stated in the present specification, it is routinely utilized in the art as a target peptide carrier for immunization protocols at the time the present priority applications were filed. The present specification supports claim 69 for the same reason that it supports claim 63 as discussed above.

Support for new claims 69-91

Support for claims 69-85 and 88-91 can be found, *inter alia*, at page 12, line 8 to page 13, line 4 (*See* also page 8, line 24 to page 9, line 7). The present specification teaches antibodies that inherently recognize and bind, and/or specifically bind, the bioactive, three-dimensional epitope of PTH. *See* the above discussion for claim 47. Such antibodies are selective for bioactive PTH. In a particular embodiment, the antibodies are inherently capable of recognizing and binding the three-dimensional epitope of PTH comprising the amino terminus, and/or PTH_{1-13}. The PTH protein can be a human PTH protein. SEQ ID NO: 1 sets out a peptide sequence having Ser in position 1 and Lys in position 13, and it would be obvious to produce antibodies to this segment of PTH based on the present disclosure. The term "immunoreactive" provides another term for binding of an antibody to an antigen, thus the present specification teaches antibodies that are immunoreactive with the bioactive amino-terminal portion of human PTH, and antibodies that are immunoreactive with PTH_{1-13}. The present specification further teaches

both polyclonal and monoclonal antibodies, and coupling these antibodies with detectable markers. And, although the present specification does not specifically teach the use of a pharmaceutically acceptable carrier with the described PTH antibodies, it would have been obvious to one of skill in the art to provide such a combination based on the present disclosure. Moreover, although the present specification does not specifically describe that the present antibodies reduce adenylate cyclase activity by binding the bioactive portion of PTH, such functionality comprises an inherent characteristic of the antibodies taught in the present specification.

Support for claim 86 can be found, *inter alia*, at page 11, line 7 to page 13, line 4 of the present specification (*See* also page 8, line 24 to page 9, line 18 of the '422 application), which teaches initial immunization together with a booster immunization to generate antibodies to PTH antigen, and thereafter recovering the antibodies. *See also*, page 12, lines 8-22 of the present specification, which teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH), *i.e.*, between about 5,000 and 10,000,000 (*see also* page 8, line 24 to page 9, line 7 of the '422 application). As indicated above, KLH was routinely utilized in the art as a target peptide carrier for immunization protocols at the time the presently claimed priority applications were filed.

The present specification teaches immunization with PTH coupled to a protein carrier, together with a second booster immunization to generate antibodies to the PTH antigen, and thereafter recovering the antibodies. As indicated above, these antibodies inherently recognize and bind the bioactive, three-dimensional epitope of PTH.

Support for claim 87 can be found, *inter alia*, at page 11, line 7 to page 13, line 4 of the present specification (*See also* page 8, line 24 to page 9, line 18 of the '422 application), which teaches initial immunization together with a booster immunization to generate antibodies to PTH antigen, and thereafter recovering the antibodies. *See also*, page 12, lines 8-22 of the present

specification, which teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH), *i.e.*, between about 5,000 and 10,000,000 (*see also* page 8, line 24 to page 9, line 7 of the '422 application). As indicated above, KLH was routinely utilized in the art as a target peptide carrier for immunization protocols at the time the presently claimed priority applications were filed.

The present specification teaches immunization with whole PTH coupled to a protein carrier, together with a second booster immunization to generate antibodies to the PTH antigen, and thereafter recovering the antibodies. As indicated above, the present specification teaches a method for producing and recovering antibodies that inherently recognize and bind the bioactive, three-dimensional epitope of PTH comprising PTH_{1-13}. *See supra.*

Support for new claims 92-97

Support for claim 92-97 can be found, *inter alia*, at page 6, lines 5-8; page 9, line 14 to page 13, line 4 of the present specification (*See also* page 4, lines 11-14; page 6, line 5 to page 9, line 18 in the '422 application). As indicated above, the present specification teaches antibodies that inherently recognize and bind the bioactive, three-dimensional epitope of PTH comprising PTH_{1-13}. Although kits are not specifically listed in the present application, general PTH assays containing PTH specific antibodies are provided. All components necessary for practicing the PTH assays taught in the present application are provided and one of skill in the art would understand that a kit comprising these components would be obvious and desired based on the present disclosure. As for tools to acquire a biological sample, such tools are standard in the art and inherently necessary to obtain a sample to practice the present methods. Moreover, although an acridinium ester is not specifically provided in the present disclosure, it provides one exemplary chemiluminescent agent that is well known in the art. The use of such a detectable label would be obvious in light of the present disclosure.

Support for new claims 98-107

Support for claims 98-100, 103-105 can be found, *inter alia*, at page 2, lines 21-26; page 4, line 24 page 5, line 9; page 9, line 14 to page 11, line 4 of the present specification (*See* also page 6, line 5 to page 7, line 23) which teaches a method for detecting cyclase active PTH by exposing a sample to an antibody that binds the cyclase activating epitope of PTH, and detecting the PTH/antibody complex. The antibody can also be labeled to aid in the detection. In addition, the present disclosure teaches the use of a second antibody to also bind the PTH peptide prior to detection of the antibody/PTH complex. Although hypoparathyroidism itself is not specifically exemplified, obtaining and measuring samples from patients having pseudohypoparathyroidism is exemplified. Notably, pseudohypoparathyroidism represents one form of hypoparathyroidism. *See, e.g.*, T. Yasuda, H. Niimi, *Acta Paediatr Jpn.* Aug;39(4):485-90 (1997) (abstract) (attached as Exhibit F).

Support for claims 101-105 can be found, *inter alia*, at page 2, lines 21-26; page 4, line 24 page 5, line 9; page 6, lines 5-10; page 9, line 14 to page 11, line 4 of the present specification (*See* also page 2, lines 2-14; page 4, lines 11-16; page 6, line 5 to page 7, line 23) which teaches a method for detecting cyclase active PTH by exposing a sample to a capture antibody that binds the cyclase activating epitope of PTH, exposing the sample to a second antibody that binds to different epitope than the capture antibody, and detecting the PTH/antibody complex. The detection antibody can also be coupled with a chemiluminescent marker to aid in the detection. Moreover, although an acridinium ester is not specifically provided in the present disclosure, it provides one exemplary chemiluminescent agent that is well known in the art. The use of such a detectable label would be obvious in light of the present disclosure. Although hypoparathyroidism itself not specifically exemplified, obtaining and measuring samples from patients having pseudohypoparathyroidism is exemplified. As indicated above, pseudohypoparathyroidism is one form of hypoparathyroidism.

Support for claims 106-107 can be found, *inter alia*, at page at page 11, line 8 to page 13, line 4 of the present specification (*See* also page 8, line 24 to page 9, line 7). Clearly, the present specification teaches immunoassays comprising antibodies that recognize and bind the bioactive amino terminus of PTH, even when that amino terminus comprises PTH_{1-13}.

Accordingly, it is submitted that new claims 47-107 have support in the present application.

Claims pending in U.S. Application No. 09/898,398 as of May 1, 2003

U.S. Application No. 09/898,398 published on May 1, 2003. The current applicant appreciates that prosecution is ongoing in connection with U.S. Application No. 09/898,398 (the '398 application) such that the claim status therein is in a state of flux. In particular, the current applicant is aware that on September 10, 2001, the applicants in connection with the '398 application submitted a preliminary amendment. The substance of this September 10, 2001 amendment is unknown to the current applicant. Nevertheless, in order to preserve rights under 35 U.S.C. 135(2)(b), the current applicant has included claims directed to the same invention as that encompassed by the claims pending in the '398 application prior to the preliminary amendment of September 10, 2001. If the Office deems it appropriate under the circumstances, the current applicant would be receptive to the suggestion of claims directed to the same invention as that currently pending in the '398 application, if such claims have been amended from their state as they were prior to September 10, 2001.

Proposed counts between claims 47-107 of the present application and pending claims of the '398 application

Out of concern for easing the burden on the Patent Office, the Applicants set forth the proposed counts as comprising the independent claims. Notably all claims published in U.S. Application No. 09/898,398 (published as US 2003/0082179 A1) are identically copied herein.

The following table sets forth the counts and claims corresponding to the counts in both the present application and U.S. Application No. 09/898,398.

Count	Present claim number	U.S. Application No. 09/898,398 claim number
1	47	1
2	55	9
3	64	18
4	67	21
5	69	23
6	73	27
7	75	29
8	85	39
9	86	40
10	87	41
11	88	42
12	89	43
13	90	44
14	91	45
15	92	46
16	98	52
17	101	55
18	106	60

Accordingly, the present application is claiming the same invention as that set forth in U.S. Application No. 09/898,398.

CONCLUSION

It is respectfully submitted that new claims 47-107 of the present application are fully supported by the specification and claims as originally filed and entry of new claims 47-107 is respectfully requested. It is further respectfully submitted that claims 47-107 of the present application and claims 1-61 of the '398 application are drawn to the same invention. It is respectfully requested that an interference be declared between claims 47-107 of the present application and claims 1-61 of the '398 application.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing 532212000624. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 16, 2004

Respectfully submitted,

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